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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,832	07/10/2000	SUZANNE CORY	017227/0159	3471

7590 08/23/2002

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EXAMINER	
YU, MISOOK	
ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 08/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/508,832	Applicant(s) CORY ET AL.	
	Examin r Misook Yu	Art Unit 1642	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44 and 51-61* is/are pending in the application.

4a) Of the above claim(s) *2-5,10-20,23-27,29-44 and 51-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-9,21,22,28 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group V (claims 1, 6-9, 21-28, 61 drawn to SEQ ID NO:9 encoding SEQ ID NO: 10, which is a isolated DNA encoding human BimEL) in Paper No. 14 is acknowledged.

There are several grounds for the traversal:

i. The traversal for requesting rejoining of groups V and X is on the ground(s) that: (a) restriction between protein and DNA under PCT rules is improper; (b) the Examiner made error by indicating that SEQ ID NO:10 is encoded by SEQ ID NO:7, which leads applicant to say "Applicants elect Group X with the understanding that it is the Group which reads on SEQ ID NO:9"; (c) since applicant amends the claims the reference cited by the Examiner in the prior Office Action (Paper No. 10) is no longer prior art and the prior art cited by the Examiner is not quite what applicant is claiming in the instant application.

ii. The traversal for requesting rejoining of groups V and I-IV is on the ground(s) that: the three different splice variants from mouse and the different splice variants from human (total 6 different products) are related products and search for up to 10 nucleic molecules are accepted practices in the Patent Office. The traversal for requesting rejoining of groups X and VI-IX is on the ground(s) that: all of the six products are capable of using together and similar products.

iii. The traversal for requesting rejoining of groups V or X and XI-XXII is on the ground(s) that: they are products and method of using the products.

iv. The traversal for requesting withdrawal of election of species in groups IX and X (Item 6) is on the ground(s) that: searching is not burdensome.

v. The traversal for requesting withdrawal of election of species in groups I-V (Item 7) is on the ground(s) that: claims 21 and 22 have only one species, instead of two species.

On reconsideration, the species election requirement for groups I-V (v above) will be withdrawn and all of species drawn to SEQ ID NO:9 will be examined on merits whether the species bind to or not bind to a dynein light chain.

However, all other Restriction Requirements and Species Election Requirement are maintained because applicant's argument above is not found persuasive for reasons set forth in the Restriction Requirement in Paper 14 and for the following reasons: A national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. When claims to different categories (i.e., three different proteins from different species for the instant application) are present in the application, the claims will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories: (1) A product and a process specially adapted for the manufacture of said product; or (2) A product and a process of use of said product; or (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or (4) A process and an apparatus or means specifically designed for carrying out the said process; or (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(b) and (d). Group I will be the main invention. After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).)

As for the examiner's error on indicating the SEQ ID NO:10 is encoded by SEQ ID NO:7 is error but groups V and X cannot be rejoined because the first

claim still reads on any nucleic acid encoding a protein that induce apoptosis. Therefore the error is irrelevant in Restriction Requirement. The examiner in the prior Office Action (Restriction Requirement) indicated that the first invention as written does not contribute over the prior art, therefore a protein encoded by the first invention is not joined with the first invention, which is DNA molecules. Applicant amended claims, but the amended claim 1 is still reads on DNA encoding a (any) derivative that induces apoptosis and Oltvai et al (1993, Cell 74, 609-19) teach DNA molecule encoding a protein (derivative) that induce apoptosis. See also below in Written Description and New Matter Rejection below. Therefore, the amended claims still lack a technical feature that defines a contribution over the prior art.

Examination of up to 10 sequences does not apply to instant application because the sequences are paterntably different products, i.e. products encoding proteins with different biological activities and proteins encoded by the products.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-44 and 51-61 are pending and applicant elected group V (claims 1, 6-9, 21-28, and 61). Claims 2-5, 10-20, 23-27, 29-44, 51-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b). This examiner notes that claims 23-27 was included in the elected group V in Paper No. 14 but the claims are drawn to non-elected inventions, murine BimEL, or BimL respectively. Therefore it is also withdrawn from further consideration in light of applicant's election of claims drawn to SEQ ID NO:9. Applicant timely traversed the restriction (election) requirement in Paper No. 14.

Claims 1, 6-9, 21, 22, 28, and 61 are examined on merits as drawn to SEQ ID NO:9 encoding SEQ ID NO:10, a human BimEL.

Specification

Claims 6-9, 21, 22, 28, and 61 are objected to because of the following informalities: the claims have not been amended to reflect the elected invention. Appropriate correction is required.

Claim 61 is objected to because of the following informalities: the claim depends on a non-elected claim. Appropriate correction is required.

For this office action, however, the limitation of claim 60 will be included in examination of claim 61. However, this treatment does not relieve applicant the burden of responding to this objection.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example at page 20, the last line. Applicant is requested to carefully review the whole application for further embedded hyperlink and/or other form of browser-executable code in the application and Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The disclosure is objected to because of the following informalities: The specification at page 63, lines 13 and 14 alleges that Table 1 of the instant specification should have shown colony formation data but the actual Table 1 of the specification at page 14 is a list of single and triple letter amino acids abbreviations.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6-9, 21, 22, and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 6-8, and 61 recite "a derivative" but it is not clear what the metes and bounds are for the term. What is claimed by the term for patent protection? Is a derivative related to the SEQ ID NO:9 protein by function or structure, both, or neither? The specification does not define the term. The description of derivative at page 23 lines 10-28 does define the metes and bounds of what is

claimed by the term. In fact, based on the description, one of ordinary skill would interpret "derivative" in the instant claims would include any and all of proteins.

Claims 1, and 6-8 recite "homologue thereof" and claim 61 refers to non-elected claim 60 which recites "homologue thereof" but it is not clear what the metes and bounds are for the phrase.

Claim 1 recites "a polypeptide having one or more of the identifying characteristics of Bim or derivative or homologoue thereof" but it is not clear what the metes and bounds are for the phrase. The claim define only one functional characteristics of a product, i.e., apoptosis. Is there any more identifying characteristics? The specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 6 recites "an amino acid sequence substantially as set forth in one of SEQ ID NO:8 or 10" but it is not clear what the metes and bounds are for the phrase. Is the phrase mean an amino acid sequence similar to SEQ ID NO: 9? Why "substantially" is in front of "as set forth"? What term(s) or phrase in the claim is/are modified by the term "substantially"?

Claim 7 recites "a nucleotide sequence substantially as set forth in SEQ ID NO:7 or 9" but it is not clear what the metes and bounds are for the phrase. What term(s) or phrase in the claim is/are modified by the term "substantially"?

Claim 7 recites "under low stringency conditions" but it is not clear what the metes and bounds are for the term. The term "under low stringency conditions" is not defined by the claim, the specification in the paragraph bridging pages 21 and 22 does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 8 and 9 recite "substantially set forth" but it is not clear what the metes and bounds are for the phrase.

Claim 61 recites "peptide" but it is not clear what the metes and bounds are for the term. The term is not defined by the claim or the specification. Is the

peptide recited in claims 61 different from a polypeptide recited in claim 1? If so, then how is a peptide recited in claim 61 different from a polypeptide recited in claim 1? Is there any differences in length of amino acids?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, and 6-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had ***possession*** of the claimed invention. The claims are drawn to a genus of isolated DNA molecules encoding a polypeptide having one or more of the identifying characteristics of human BimEL (SEQ ID NO:9 encodes SEQ ID NO:10, i.e. the elected invention, see page 58 of the specification) capable of inducing apoptosis.

The specification teaches both human and murine Bim genes encode three different products with different molecular structures as evidenced by different SEQ ID NOs and different biological functions: ***1)*** Figure 1 shows that schematic structures of BimS, BimL, and BimEL; ***2)*** Figure 2 shows Bim mRNA expression, Figure 3 shows (Example 2 further explains findings of Figure 3) BimL localizes to cytoplasmic membranes and Bcl-2 does not disrupt the localization; ***3)*** Figure 4, and Examples 3 and 4 disclose overexpression of BimL (species not clear whether it is human or murine) kills cells and appears to die from apoptosis and expression of wt-Bcl-2 reverses the apoptotic process; ***4)*** Example 5 (page 63) and Figure 6 disclose human Bcl-2 is able to bind all three variants and either gamma irradiation or IL-3 deprivation causes cells expressing the dual pair (human Bcl-2 and BimS) die quicker than the parental cells. However the cells expressing either the dual pair (Bcl-2 and BimL) or the dual pair (Bcl-2 and BimEL) dies slower than the parental cell lines (see Figure 6C); ***5)***

Example 6 (page 63) says Bim does not interact with Bax but BimL binds to wt-Bcl-XL (Fig. 7A) and Bcl-w (Fig. 7B), but it does not bind the Bcl-2 mutants used in the study shown in (Figure 7A), or other virally encoded Bcl-2 homologues; ***6)*** Figure 7 disclose BimL is involved in apoptosis, and; ***7)*** Figure 8 and Example 7 (page 64) does not show any data with the elected species (human BimEL) but disclose BH3 domain of BimL is essential for interaction of Bcl-2 and for promoting apoptosis; ***8)*** Examples 9 and 10 (page 66) disclose the DNA constructs used in the experiments but do not disclose which cDNA (human, murine, or both) was used. It appears that mouse BimL was purified and the purified protein was used to make Bim-specific antibody (see page 71 lines 24-30); ***9)*** Example 14 (page 74) says that murine BimS does not bind a dynein light chain but BH domain deletion mutant made from [BimEL] binds to the dynein light chain (lines 16 and 17 of page 74). D51, K52, S53, T54 residues of BimL are important for murine (?) BimL to bind to the dynein light chain because S53P, T54A, or T54I/N65S mutant had binding activity less than 0.1 % of that of the wild type BimL and D52G mutant also had reduced the binding activity to 5-10 % of the wild type BimL.

The summary of the disclosure in the specification is: Most of the data disclosed involve apoptotic activity of BimL and the single and double point mutation analysis for dynein light chain binding activity (see 9) above) disclosed also involve activity of murine BimL, not human BimEL. It is not clear from the disclosure in the specification if any of those single and double point mutants of BimL is able to induce apoptosis. The specification says that deletion of BH domain of BimEL does not affect binding of a dynein light chain.

The specification provides evidence for SEQ ID NO:9 encoding SEQ ID NO:10, a human BimEL which has potential to induce apoptosis although the specification does not explicitly show the data. The specification does not describe any mutant of SEQ ID NO:10 capable of inducing apoptosis. Based on only one species, one cannot predict the types of additional species of human BimBL, for example, polymorphic variants, which has apoptotic activity. Since

the genus includes a large number of unpredictable species, possession of only one species is not seen as sufficient to reasonably convey possession of the entire genus. It is concluded that applicants describes SEQ ID NO:9 encoding SEQ ID NO:10 with potential for apoptotic activity.

Claims 21, 22, and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had ***possession*** of the claimed invention. The claims are drawn to a genus of isolated DNA molecules, termed as "a variant" encoding a polypeptide having one or more of the identifying characteristics of human BimEL, wherein the polypeptides encoded by the claimed invention have apoptotic activity but cannot bind a dynein light chain.

This examiner notes, as discussed above in rejection of claims 1, and 6-9 under Written Description, the specification discloses several single and double point BimL (which is patentably distinct product from the elected invention) mutants cannot bind to a dynein light chain. However, the specification does not describe any DNA molecule that has structural similarities to SEQ ID NO:9, and encodes a protein capable of inducing apoptosis, but cannot bind a dynein light chain. The specification does not disclose any humanEL mutant that has apoptotic activity but cannot bind a dynein light chain.

Claims 21, 22, 28, and 61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to ***enable*** one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to a isolated DNA molecules encoding a polypeptide having one or more of the identifying characteristics of human BimEL, wherein the polypeptides encoded by the claimed invention have apoptotic activity but cannot bind a dynein light chain.

One cannot extrapolate the teaching of the specification to the claims because it is well known in the art that even slight modifications in a peptide or protein structure can have significant and unpredictable effects on biological activity. Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out biological activity and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid (including conservative substitutions) in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or even with conservative glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

The specification says that BH3 domain is essential for apoptosis (Example 7) but the mutant with deletion of the entire BH3 domain still retains

apoptotic activity although the activity is reduced compared to wild type BimEL. Note Table 1 of O'connor et al, (1998, The EMBO Journal, Vol. 17, pages 384-395). Further, the specification does not teach any other specific structures responsible for apoptosis, nor provide guidance as to what changes in the structure can be made retaining apoptotic activity while abolishing the dynein light-chain-binding ability of human BimEL. This examiner notes, as discussed above under rejection of claims 21, 22, and 28 under Written Description, the specification discloses several single and double point BimL (which is patentably distinct product from the elected invention) mutants cannot bind to a dynein light chain. However, it is not clear whether those mutants that cannot bind a dynein light chain induce apoptosis. Even if those mutants that cannot bind a dynein light chain induces apoptosis, one cannot extrapolate the teaching of the specification to the claims because the specification at Fig. 6C teaches that biological functions of one splicing variant of Bim is not same as those of the other variants. The longer splicing variants have all of the amino acids in the shortest splicing variant, however the shortest splicing variant have the best apoptotic activity. This suggests that it requires more than the identity of primary amino acids to predict the functions of Bim and the specification does not give any guidance what changes in the primary amino acids of SEQ ID NO:10 could be made to retain apoptotic activity but not to retain a dynein-light-chain binding activity.

The specification provides insufficient guidance, and provides no working examples of human BimEL mutant or variant that has apoptotic activity but cannot bind to a dynein light chain. Considering lack of working examples, insufficient guidance, unpredictability in art, it is concluded in that undue experimentation is necessary to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Claims 1, 6-9, and 61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for how to make SEQ ID NO:9

DNA that encodes SEQ ID NO:10, a human BimEL with potential to induce apoptosis, does not reasonably provide enablement for any other isolated DNA molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to isolated DNA molecules with varying degrees of structural similarities to SEQ ID NO:9 which encode polypeptides similar to SEQ ID NO: 10, wherein the polypeptides encoded by instantly claimed invention all have apoptotic activity (claims 1, 6-9). Claim 61 is drawn to an isolated DNA molecule encoding any peptide at least bigger than 4 contiguous amino acids of SEQ ID NO:10

The specification discloses that SEQ ID NO:9 encodes a full-length human BimEL protein with potential to possess apoptotic activity as discussed in the Written Description above, however, the specification does not teaches any other isolated DNA molecules with similarity to SEQ ID NO:9, wherein the DNA encoding a protein able to induce apoptosis. The specification does not teach any method of using any peptide (encoded by SEQ ID NO:9) that does not posses apoptotic activity.

The specification teaches both human and murine Bim genes encode three different products with different molecular structures and different biological functions: ***1)*** Figure 1 shows that schematic structures of BimS, BimL, and BimEL; ***2)*** Figure 2 shows Bim mRNA expression, Figure 3 shows (Example 2 further explains findings of Figure 3) BimL localizes to cytoplasmic membranes and Bcl-2 does not disrupt the localization; ***3)*** Figure 4, and Examples 3 and 4 disclose overexpression of BimL (species not clear whether it is human or murine) kills cells and appears to die from apoptosis and expression of wt-Bcl-2 reverses the apoptotic process; ***4)*** Example 5 (page 63) and Figure 6 disclose human Bcl-2 is able to bind all three variants and either gamma irradiation or IL-3 deprivation causes cells expressing the dual pair (human Bcl-2 and BimS) die quicker than the parental cells. However the cells expressing either the dual pair

(Bcl-2 and BimL) or the dual pair (Bcl-2 and BimEL) dies slower than the parental cell lines (see Figure 6C); ***5)*** Example 6 (page 63) says Bim does not interact with Bax but BimL binds to wt-Bcl-XL (Fig. 7A) and Bcl-w (Fig. 7B), but it does not bind the Bcl-2 mutants used in the study shown in (Figure 7A), or other virally encoded Bcl-2 homologues; ***6)*** Figure 7 disclose BimL is involved in apoptosis, and; ***7)*** Figure 8 and Example 7 (page 64) does not show any data with the elected species (human BimEL) but disclose BH3 domain of BimL is essential for interaction of Bcl-2 and for promoting apoptosis; ***8)*** Examples 9 and 10 (page 66) discuss the DNA constructs used in the experiments but do not disclose which cDNA (human, murine, or both) was used. It appears that mouse BimL was purified and the purified protein was used to make Bim-specific antibody (see page 71 lines 24-30); ***9)*** Example 14 (page 74) says that murine BimS does not bind a dynein light chain but BH domain deletion mutant made from [BimEL] binds to the dynein light chain (lines 16 and 17 of page 74). D51, K52, S53, T54 residues of BimL are important for murine (?) BimL to bind to the dynein light chain because S53P, T54A, or T54I/N65S mutant had binding activity less than 0.1 % of that of the wild type BimL and D52G mutant also had reduced the binding activity to 5-10 % of the wild type BimL.

One cannot extrapolate the teaching of the specification to the claims because it is well known in the art that even slight modifications in a peptide or protein structure can have significant and unpredictable effects on biological activity and one cannot extrapolate functions of BimS or BimL to the functions of BimEL since the specification clearly teaches that biological functions of the three different splicing variants are different as discussed above in the rejection of claims 21, 22, 28, and 61 under Enablement.

The specification does not teach any other specific structures responsible for apoptosis, nor provide guidance as to what changes in the structure can be made retaining apoptotic activity. The specification does not provide any guidance how to use a peptide that does not have apoptotic activity. The

specification provides insufficient guidance, and provides no working examples of human BimEL mutant or variant that has apoptotic activity.

Considering lack of examples and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to practice the full scope of the claimed invention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 6-9, 21, 22, 28, and 61 are rejected under 35 U.S.C. 101 because the claims read on the proteins which is found in nature and thus, is unpatentable to applicant. It is suggested that applicant use the language "isolated" or "purified" in connection with the nucleic molecules to identify products that are not found in nature. Consequently, the claims do not embody patentable subject matter as defined in 35 U.S.C. 101.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Oltvai et al (27 August 1993, Cell 74, 609-619).

Claim 1 is drawn to an isolated DNA encoding protein that has indefinable structural characteristics (see page 23 lines 10-28, especially lined 3 and 4, of

the specification) to human BimEL. Claim 1 is interpreted as drawn to any nucleic acid molecules that encode a polypeptide capable of inducing apoptosis and claim 61 is drawn to an isolated DNA molecule that encodes at least 4 contiguous amino acids of SEQ ID NO:10. Oltvai et al (27 August 1993, Cell 74, 609-619) in Figure 2 (page 611) teaches a cDNA sequence which encode Bax beta capable of inducing apoptosis and also teaches an isolated DNA molecule that encodes RIGDE (amino acids #66-70 of Bax beta), which is identical to RIGDE, amino acids #150-154 of human BimEL. Also note Figure 9A of the instant application.

Thus, Oltvai et al anticipate claims 1 and 61.

Conclusion

No claim is allowed.

An isolated DNA molecule comprising SEQ ID NO:9 is free of prior art. Applicant is request to points to the support for apoptotic activity of SEQ ID NO:10 encoded by SEQ ID NO:9, not by SEQ ID NO:5 (murine BimEL). Note page 58 of the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Misook Yu whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
August 19, 2002

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800
1600